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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 10/510,912

Filing Date: October 08, 2004

Appellant(s): FLORES ET AL.

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Melissa B. Wenk  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed July 3, 2008 appealing from the Office action mailed November 30, 2007.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

De Francesco et al., WO 02/059321, August 2002.

Rice et al. (“Rice II”), WO 01/89364, November 2001

Copending application 10/543,633, Grobler et al., filed July 28, 2005.

6,297,003	Rice et al. (“Rice I”)	10-2001
6,063,562	Melnick et al.	5-2000
20040018529	Li et al.	1-2004
5,783,669	Hawkins et al.	7-1998

## **(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 19-20, 28, 29, 31-34, 37, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Francesco in view of Rice I and Rice II; and further in view of Melnick and of Li.

The claims are drawn to an HCV replicon comprising at least two regions from different HCV strains, wherein at least one of the regions comprises the 3' UTR from HCV subtype 1a. Claims 20, 21, and 31-38 require that the replicon comprises a second region consisting of a non-structural region from a clinical isolate of HCV. Claims 28, 29, 33, 34, 37, and 38 require that the replicon comprises a beta-lactamase reporter sequence, with claims 29, 34, and 38 additionally requiring that the replicon does not comprise a gene for resistance to an agent inhibiting cell growth (e.g. an antibiotic resistance gene). Claims 31 and 32 require that the non-structural region comprises an HCV NS5B polymerase.

De Francesco teaches an HCV replicon comprising a reporter, such as beta-lactamase. Claims 5 and 6, and page 12. The reference also indicates that the replicon may independently

include reporter or selection (i.e. sequences coding for resistance to growth inhibition agents) sequences, and therefore indicates that a replicon comprising one of the two need not include the other. See e.g., pages 11, lines 22-26. The reference therefore teaches HCV replicons comprising a reporter which do not also contain a sequence coding for a resistance gene such as is required by claim 34. The reference also teaches that the replicons comprise an HCV 3' UTR sequence, and indicates that any such sequence may be used. Page 10, lines 23-30. On pages 10-11, De Francesco also indicates that the non-structural protein sequences used in the replicon may include proteins, including NS5B proteins, from different HCV strains. However, the reference does not specifically teach or suggest the use of a HCV 3' UTR sequence from an HCV subtype 1a sequence, or specify the use of an NS5B protein from a clinical isolate.

Rice I teaches the sequences of several HCV 3' UTRs, including the sequences of several variants of the HCV 1a isolate H77. See e.g., Figure 3, and column 11 (lines 20-25). The reference also indicates that such sequences would be useful for the construction of HCV replicons which could be used for screening for inhibitors of HCV replication. Columns 21 (lines 23-33) and 30 (lines 11-14). From these teachings, it would have been obvious to those of ordinary skill in the art to use the 3' UTRs of Rice I for the production of HCV replicons as suggested by De Francesco. Those of ordinary skill in the art would have been motivated to make such a substitution because the art indicates that the 3' UTRs of Rice I are functional equivalents for the UTR sequences provided in De Francesco with respect to their use in the construction of HCV replicons. See e.g., MPEP 2144.06. Those of ordinary skill in the art would have had a reasonable expectation of success in making such substitutions based on the

indication of De Francesco that any HCV 3' sequence could be used, and suggestion of the use of the 1a sequences in Rice I.

Rice I also does not teach or suggest the use of a sequence encoding an HCV NS5B protein from a clinical isolate. However, as was indicated above, De Francesco does suggest the use of NS5B sequences from different strains. In addition, the Rice II reference also provides teachings relating to HCV replicons, and indicates both that the replicons may comprise sequence form any HCV subtype (pages 20-21), and that the proteins encoded by the replicons may be from different isolates of HCV, including embodiments wherein one of the proteins in the encoded polyprotein is from a different subtype or strain. Pages 17 (lines 21-26) and 23 (lines 31-34). While the reference does not specifically teach the insertion of nucleotide sequences from clinical isolates, such would have been obvious to those of ordinary skill in the art from the teachings found therein.

For example, the Rice II reference teaches that the replicons may be used to screen for anti-viral drugs, and indicates that wild-type forms of the targets for such drugs should be used. Page 32, lines 26-30. The reference also states "in a chronically infected individual, changes in the virus population occur over time...; and these changes may have important consequences for disease." Page 7. Other teachings in the art also indicate that those of ordinary skill in the art would be particularly concerned with the identification of drugs that are effective against clinical isolates of pathogens, or the development of resistance in target pathogenic populations that change over time. See e.g., Melnick, column 11(lines 6-13); and Li, paragraph [0009]. While the teachings of these two references are directed to other enzymes, or to HIV enzymes, those of ordinary skill in the art of treating HCV would have looked to such teachings as similar problems

would be seen with HCV as indicated by the teachings of Rice II. These teachings therefore suggest to those of ordinary skill in the art the screening of anti-HCV drugs against HCV isolates from patients during the coarse of infection to determine 1) if changes have arisen in the HCV population rendering them resistant to the drug, and 2) screening the target genes of HCV populations from an infected patient against different drugs if such resistance has arisen. In either case, the teachings suggest the use of replicons comprising HCV protein coding regions from an infected patient for use in such screening.

Thus, based on the teachings of the cited references, and the knowledge in the art, it would have been obvious to those of ordinary skill in the art to have substituted NS5B proteins from HCV clinical isolates into an HCV replicon for the purpose of screening for inhibitors effective against such isolates, or for the detection of anti-viral resistance in such isolates. The combined teachings of these references therefore render the claimed inventions obvious.

2. Claims 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Francesco in view of Rice I, Rice II, Melnick, and Li as applied to claims 18-20, 28, 29, 31-4, 37, and 38 above, and further in view of Hawkins. These claims describe the previously described replicons as further comprising the presence of silent modifications to the replicon's nucleotide sequence which result in the presence of restriction sites not present in a naturally occurring HCV.

The teachings of De Francesco have been described above. This reference teaches the making of adaptive mutations to the replicon sequences, as well as combining such mutations to other mutations that do no inhibit replicon activity. Moreover, Rice II teaches both the

substitution of a single protein within the replicon, and indicates that such may be accomplished by modification of the replicon sequence to include restriction sites convenient for subsequence engineering. Pages 23 (lines 31-34) and 22 (lines 20-28). However, neither of these references specifically teaches the use of silent mutations for the creation of restriction sites up- and downstream of a target region.

Nonetheless, such modifications would have been obvious to those of ordinary skill in the art. This is because, as is indicated by Rice II, it was known in the art to make such substitutions to optimize the insertion or cloning of sequences into viral or plasmid vectors. See also, Hawkins, column 5, lines 8-12. In addition, it is noted that the teachings of Hawkins specifically indicate that it was known by those of ordinary skill in the art to make such modifications through the use of silent nucleotide substitutions which take advantage of the redundancy in the genetic code. Id. In view of such knowledge in the art, and the suggestion by the teachings of the previously cited references to make chimeric HCV replicons wherein specific sequences are substituted for sequences of other HCV isolates, it would have been obvious to those of ordinary skill in the art to have used such a means for the cloning of the alternative HCV sequences into the chimeric replicons suggested by De Francesco and WO 01/89364. The combined teachings of these references therefore render the claimed inventions obvious.

3. Claims 19, 20, 28, 29, 31-34, 37, and 38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19 and 20 of copending Application No. 10/543,633.. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application read

on particular replicons that meet the present claim limitations. It is noted that, although the original rejection of the present claims was based on claims 9 and 10 of the copending application, the subject matter on which the rejection was based was removed from claims 9 and 10, and resubmitted in claims 19 and 20 as indicated in the Advisory action of March 26, 2008

In particular, the rejected claims read on chimeric HCV replicons comprising at least 2 HCV regions from different HCV strains , wherein at least one of the regions is an HCV 1a 3' UTR. Claims 20, 31, and 32 further require that the replicon comprises a non-structural regions, esp. NS5B, from a clinical isolate of HCV. Claims 28, 29, 33, 37, and 38 require that the replicon comprising a beta-lactamase reporter, preferably in the absence of a gene conferring resistance to an agent that inhibits cell growth (e.g. an antibiotic resistance gene).

The copending claims are drawn to an HCV replicon meeting these limitations. In particular, the copending claims are drawn to an HCV replicon comprising SEQ ID NO: 4 of that application. Page 16 of the copending application teaches that the BK replicon of SEQ ID NO: 4 is a chimeric replicon comprising a beta-lactamase reporter, no selection gene, and having an HCV 1a 3' UTR sequence, and comprising non-structural regions from a clinical isolate. The claims of the copending application would therefore anticipate the present claims if applied as prior art. Thus, the present claims are rejected for obviousness type double patenting over the copending claims.

#### **(10) Response to Argument**

1. The rejection of claims 19-20, 28, 29, 31-34, 37, and 38 as obvious over the teachings of De Francesco in view of Rice I, Rice II, and further in view of Melnick and Li; and the rejection

of claims 35-36 as obvious over the teachings of the above references, further in view of Hawkins should be affirmed.

The Appellant relies on substantially the same arguments for each of these two rejections. The arguments in traversal of the rejections will therefore be considered together. AS the sole additional argument presented with respect to the second ground of rejection is that the additional secondary reference does not cure the asserted deficiencies of the references cited in the first ground of rejection, the two rejections should stand or fall together. Appellant provides five grounds of traversal for these rejections.

The first two arguments apply to the claims generally.

Appellant first asserts that “broad, generic disclosures are inadequate to establish obviousness of a species,” and that the cited references therefore fail to render the claimed species obvious. This argument should not be found persuasive because the teachings of the cited prior art render obvious not only a genus replicons comprising “any naturally occurring UTR,” but also replicons comprising those specific UTR sequences disclosed by the Rice I reference, including the HCV 1a UTRs disclosed therein.

Appellant's argument appears to be based in part of the Federal Circuit decision of In re Jones, 21 U.S.P.Q.2d 1941 (1992). It is based on this case that the Appellant asserts that a generic disclosure is inadequate to render obvious a species. Even if this interpretation of the decision was applied<sup>1</sup>, the argument should not be found persuasive. This is because the facts of

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<sup>1</sup> The Jones decision does not come to the conclusion that a genus per se cannot render obvious a species. Rather, the court indicates that they refuse to agree to a rule that "that regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it." Id., at 1943. The distinction being that, by refusing to

the Jones case are distinct from those of the present case. In Jones, the court found that the art on which the rejection was based disclosed a “potentially infinite genus,” and did not specifically disclose the claimed species. In contrast, as was indicated the statement of the rejection above, while the teachings of De Francesco render obvious a genus of UTRs, the additional teachings of Rice I identify species of HCV 1a UTRs that may be used in making HCV replicons. Because Rice I identifies such species, the rejection does not rely merely on the generic teachings of De Francesco to render the claimed invention obvious.

Appellant next argues that the teachings of Rice are not limited to a disclosure of HCV 1a UTR sequences. Appellant asserts that, because Rice I teaches UTRs from other strains of HCV, and fails to single out HCV 1a UTRs from those of other HCV UTRs, the teachings of the reference fail to render obvious the use of these sequences in the replicons of De Francesco. This argument should not be found persuasive because, while the Rice I reference discloses HCV UTRs from other HCV strains, this simply indicates that it would have been obvious to those of ordinary skill in the art to have used any of such UTRs in the HCV replicons, including those of the HCV 1a strains. There is no need for the art to disclose the HCV 1a sequences as better than the other sequences as it would have been equally obvious to those of ordinary skill in the art to use any of these sequences as a functionally equivalent HCV 3' UTR for the purposes of producing an HCV replicon.

With respect to this argument, the Appellant additionally asserts that the Examiner has provided no art that describes the 3' UTRs of Rice I (from HCV 1a) as functional equivalents to

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adopt this rule, the court is not concluding that a genus may render obvious a species wherein the genus is

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the 3' UTRS of HCV con-1 (the strain used in De Francesco). The Appellant asserts that the teachings of De Francesco relied on by the Examiner, indicating that HCV replicons may be made with any naturally occurring or functionally equivalent HCV 3' UTR, does not imply that all naturally occurring HCV 3' UTRs are functional equivalents of each other. The argument should not be found persuasive because this is precisely what the teachings of De Francesco suggest.

The reference indicates that any of such naturally occurring HCV 3' UTRs may be used in the making of HCV replicons. It is therefore unclear how this teaching can be interpreted so as not to imply that the various HCV 3' UTRs are functional equivalents with respect to the making of HCV replicons. In view of this, and the fact that the Appellant provides no evidence or other support for their assertion, this argument in traversal should not be found persuasive.

The third through fifth arguments in traversal apply to those claims requiring that the HCV replicon comprises a region from a clinical isolate of the virus (i.e. claims 20 and 35-38).

The third argument in traversal is that neither the combined teachings of the cited references fail to teach or suggest replicons comprising non-structural regions from clinical isolates of HCV. In particular, the Appellant asserts that the teachings of Rice II, on which the Examiner relies in part for the rejection of these claims, nowhere refers to clinical isolates. Rather, the Appellant asserts that the teachings of the reference refer to the use of wild-type sequences, not to the use of clinical isolates.

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sufficiently narrow.

The Examiner agrees that the Rice II reference nowhere specifically refers to the use of sequences from clinical isolates for the construction of HCV replicons. It is noted that, contrary to the Appellant's arguments, the Examiner is not arguing that reference to wild-type sequences is synonymous with sequences from clinical isolates (although, the extent to which the two are distinct is not clear). A clinical isolate is understood in the art to refer to an isolate from a clinical source, such as a patient. Similarly, a wild-type HCV sequence refers to an unmodified sequence, or as Appellant asserts on page 13, to HCV sequence before "replication in cell culture" which results in the development of adaptive mutations or variants in the HCV sequence. Thus, one means for getting a wild-type sequence in which no such adaptive mutations have arisen is through the isolation of an unmodified HCV sequence from an infected patient- thus through the use of a clinical isolate. Such would have been apparent to those of ordinary skill in the art.

The rejection is based on knowledge in the art (provided e.g. by Rice II) that the sequences of HCV in infected patients changes over time, and that such changes may have consequences for the efficacy of anti-HCV therapeutics, in addition to the teachings of Rice II that protein coding regions in a HCV may be substituted with that from a different HCV isolate. From these teachings, it would have been obvious to those of ordinary skill in the art to substitute sequences in established replicons, such as those suggested by the combination of De Francesco and Rice I, with sequences from the viral populations in chronically infected patients (i.e. clinical isolates") to determine the effects of any changes in sequences of those proteins on the efficacy of drugs administered to the patient relative to that seen in the original replicon (representing what the Appellant would appear to consider the "wild-type" virus). Thus, the Examiner does not, and need not, interpret reference to wild-type sequences as identical to sequences from

clinical isolates, because the teachings of the reference provide motivation for the construction of chimeric replicons comprising sequences from clinical isolates.

The additional teachings of Li and Melnick are relied on to provide additional motivation for the construction of such replicons. I.e., to screen for antivirals effective against isolates against which the previously administered antivirals no longer work. Because these references demonstrate that it was known in the art to screen for drugs effective against modified forms of the target proteins, it would have been obvious to those of ordinary skill in the art to construct replicons comprising such modified HCV non-structural or NS5 proteins for the purpose of identifying other drugs that are effective against the changed HCV.

In either case, the rejection does not rely on an interpretation of the term wild-type that requires it to be synonymous with clinical isolate. The Appellant's argument that the Examiner applies such a meaning should therefore not be found persuasive.

The fourth argument of the Appellant is that the Examiner has applied improper hindsight in the rejections. However, the Appellant nowhere indicates where the Examiner has relied on information, or reasoning, beyond the scope of that which was available to those of ordinary skill in the art at the time of invention. In making an obviousness rejection, an examiner may rely on knowledge and motivations provided in the art. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971- indicating that it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning and that so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's

disclosure, such a reconstruction is proper). As the present rejection is based on knowledge available to those of ordinary skill in the art at the time of invention, the rationale relied upon by the Examiner is proper. This argument should therefore not be found persuasive.

Finally, the Appellant appears to be arguing that the Examiner has relied on the teachings of Melnick and Li to identify a problem to be solved, on the teachings of Rice II to provide the solution, and further asserts that the solution provided by Rice II would not result in the claimed invention. This argument should not be found persuasive. It is nowhere indicated that Rice II specifically discloses the claimed solution. Rather, it was indicated that the combined teachings in the reference would have rendered obvious the construction of a chimeric replicon wherein sequences from clinical isolates comprising modifications that have evolved during the course of infection are substituted into a "wild-type" replicon. Melnick and Li are relied upon not to identify the problem, but to provide further evidence that it would have been obvious to those of ordinary skill in the art to use such replicons to determine or identify drugs that would be effective against such changed HCV isolates. In view of the above, the Appellants argument that the Rice II reference does not specifically teach the construction of such replicons should not be found persuasive.

2. The rejection of claims 19-20, 28, 29, 31-34, 37, and 38 for obviousness type double patenting over claims 19 and 20 of copending application 10/543,633 should be affirmed.

The Appellant presents two arguments in traversal of the rejection.

The first argument is based on the description of SEQ ID NO: 1 and 3 of the copending application, which sequences comprise 3' UTR sequences from HCV 1b. However, as was indicated above, the present rejection is based on the claims drawn to SEQ ID NOS: 2 and 4 of the copending application, now claimed by claims 19 and 20 of that application. These sequences do comprise 3' UTR from HCV 1a, as noted above.

With respect to SEQ ID NOS: 2 and 4 of the copending application, the Appellant indicates only that they will consider filing a Terminal Disclaimer should the claims of one of the applications be found allowable. The statement is not an adequate response to the rejection.

The argument in traversal should therefore not be found persuasive, and the rejection affirmed.

#### **(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Primary Examiner, Art Unit 1648

Conferees:

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